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1. A method for treating or preventing a disease in a human or other mammal mediated by a VEGF-induced signal transduction pathway, comprising administering to a human or other mammal in need thereof a compound of Formula I, a salt form of a compound of Formula I, an isomer of a compound of Formula I or a prodrug of a compound of Formula I to regulate a VEGF-mediated signal transduction cascade,



wherein A is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

(iii) 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro; and

(iv) 10 membered bicyclic heteroaryl groups in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring using 3 to 4 carbon atoms, the bicyclic heteroaryl group is optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro,

B is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $-L-M$ ,  $C_1-C_5$  linear or branched alkyl,  $C_1-C_5$  linear or branched haloalkyl,  $C_1-C_3$  alkoxy, hydroxy, amino,  $C_1-C_3$  alkylamino,  $C_1-C_6$  dialkylamino, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro;

(iii) 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro; and

(iv) 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro.

L is selected from the group consisting of:

- (a)  $-(\text{CH}_2)_m\text{-O}-(\text{CH}_2)_l-$ ,
- (b)  $-(\text{CH}_2)_m-(\text{CH}_2)_l-$ ,
- (c)  $-(\text{CH}_2)_m\text{-C(O)}-(\text{CH}_2)_l-$ ,
- (d)  $-(\text{CH}_2)_m\text{-NR}^3-(\text{CH}_2)_l-$ ,
- (e)  $-(\text{CH}_2)_m\text{-NR}^3\text{C(O)}-(\text{CH}_2)_l-$ ,
- (f)  $-(\text{CH}_2)_m\text{-S}-(\text{CH}_2)_l-$ ,
- (g)  $-(\text{CH}_2)_m\text{-C(O)NR}^3-(\text{CH}_2)_l-$ ,
- (h)  $-(\text{CH}_2)_m\text{-CF}_2-(\text{CH}_2)_l-$ ,
- (i)  $-(\text{CH}_2)_m\text{-CCl}_2-(\text{CH}_2)_l-$ ,
- (j)  $-(\text{CH}_2)_m\text{-CHF}-(\text{CH}_2)_l-$ ,
- (k)  $-(\text{CH}_2)_m\text{-CH(OH)}-(\text{CH}_2)_l-$ ;
- (l)  $-(\text{CH}_2)_m\text{-C}\equiv\text{C}-(\text{CH}_2)_l-$ ;
- (m)  $-(\text{CH}_2)_m\text{-C}=\text{C}-(\text{CH}_2)_l-$ ; and
- (n) a single bond, where m and l are 0.;
- (o)  $-(\text{CH}_2)_m\text{-CR}^4\text{R}^5-(\text{CH}_2)_l-$ ;

wherein the variables m and l are integers independently selected from 0-4,

M is selected from the group consisting of :

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(iii) 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro and also oxides (e.g. =O,  $-O^-$  or  $-OH$ ); and

(iv) 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro and also oxides (e.g. =O,  $-O^-$  or  $-OH$ ).

(v) saturated and partially saturated  $C_3$ - $C_6$  monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and, nitro;

(vi) saturated and partially saturated  $C_8$ - $C_{10}$  bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro, and also oxides (e.g. =O,  $-O^-$  or  $-OH$ ); and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,

$C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro, and also oxides (e.g. =O,  $-O^-$  or  $-OH$ );

wherein each  $R^1 - R^5$  is independently selected from the group consisting of:

- (a) hydrogen,
- (b)  $C_1-C_6$  alkyl, preferably,  $C_1-C_5$  linear, branched, or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo;
- (c) phenyl;
- (d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;
- (e)  $C_1-C_3$  alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and
- (f)  $C_1-C_3$  alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo,

wherein each  $R^1 - R^5$ , when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1-C_5$  linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo,  $C_1-C_3$  alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino,  $C_1-C_3$  alkylamino,  $C_2-C_6$  dialkylamino, halogen, cyano, and nitro;

each variable  $q$  is independently selected from 0, 1, or 2; and

wherein A, B and M of formula I follow one of the following combinations:

A= phenyl, B=phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= phenyl, B=pyridinyl and M is pyridinyl, quinolinyl, isoquinolinyl or not present,

A=phenyl, B = naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=isoquinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= isoquinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= isoquinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present.

**2. (Canceled)**

3. A method as in claim 1 wherein the substituents on the groups for A, B, and M are selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl, and *tert*-butyl, F, Cl, Br, and I.

**4.-5. (Canceled)**

6. A method of claim 1 wherein the substituents of the substituted structures of B are each, independently, selected from the group consisting of methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino, diethylamino and the structure -L-M.

7. A method of claim 6 wherein the substituents of the substituted structures of A and M are each, independently, selected from the group consisting of

methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, *sec*-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino and further include:

phenyl, pyridinyl, pyrimidinyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl, chloropyridinyl, bromopyridinyl, dichloropyridinyl, dibromopyridinyl, methylphenyl, methylpyridinyl, quinolinyl, isoquinolinyl, isoindolinyl, pyrazinyl, pyridazinyl, pyrrolinyl, imidazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, benzopyridinyl, benzothiazolyl, C<sub>1</sub>-C<sub>5</sub> acyl;

NH(C<sub>1</sub>-C<sub>5</sub> alkyl, phenyl or pyridinyl), such as aminophenyl;

N(C<sub>1</sub>-C<sub>5</sub> alkyl)(C<sub>1</sub>-C<sub>5</sub> alkyl, phenyl or pyridinyl), such as diethylamino and dimethyl amino;

S(O)<sub>q</sub> (C<sub>1</sub>-C<sub>5</sub> alkyl); such as methanesulfonyl;

S(O)<sub>q</sub> H;

SO<sub>2</sub>NH<sub>2</sub>;

SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>5</sub> alkyl);

SO<sub>2</sub>N(C<sub>1</sub>-C<sub>5</sub> alkyl)(C<sub>1</sub>-C<sub>5</sub> alkyl);

NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>5</sub> alkyl); N(C<sub>1</sub>-C<sub>3</sub> alkyl) SO<sub>2</sub>(C<sub>1</sub>-C<sub>5</sub> alkyl);

CO(C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl);

C(O)H;

C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl), such as C(O)OCH<sub>3</sub>, -C(O)OCH<sub>2</sub>CH<sub>3</sub>, -C(O)OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>;

C(O)OH;

C(O)NH<sub>2</sub> (carbamoyl);

C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl), such as N-methylethyl carbamoyl, N-methyl carbamoyl, N-ethylcarbamoyl, or N-dimethylamino ethyl carbamoyl;

C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl)(C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl or pyridinyl), such as N-dimethyl carbamoyl;

C(N(C<sub>1</sub>-C<sub>5</sub> alkyl)) (C<sub>1</sub>-C<sub>5</sub> alkyl);

NHC(O)(C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl) and

N(C<sub>1</sub>-C<sub>5</sub> alkyl,)C(O)(C<sub>1</sub>-C<sub>5</sub> alkyl).

wherein each of the above substituents is optionally partially or fully halogenated.

8. A method as in claim 1 wherein A and M of formula I are independently selected from the group consisting of substituted or unsubstituted phenyl and pyridinyl.

9. A method as in claim 8 wherein B of formula I is a phenyl group, optionally substituted by halogen up to per halo and 0 to 3 times by one or more substituents selected from the group consisting of -CN, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -OH, phenyl, up to per halo substituted C<sub>1</sub>-C<sub>5</sub> alkyl, up to per halo substituted C<sub>1</sub>-C<sub>5</sub> alkoxy and up to per halo substituted phenyl.

10. (Canceled)

11. A method as in claim 1 wherein L of formula I is -O-, a single bond, -S-, -NH-, -N(CH<sub>3</sub>)-, -NHCH<sub>2</sub>-, -NC<sub>2</sub>H<sub>4</sub>-, -CH<sub>2</sub>-, -C(O)-, -CH(OH)-, -NHC(O)N(CH<sub>3</sub>)CH<sub>2</sub>-, -N(CH<sub>3</sub>)C(O)N(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)-, -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>-, -NHC(O)-, -N(CH<sub>3</sub>)C(O)-, -C(O)N(CH<sub>3</sub>)-, -C(O)NH-, -CH<sub>2</sub>O-, -CH<sub>2</sub>S-, -CH<sub>2</sub>N(CH<sub>3</sub>)-, -OCH<sub>2</sub>-, -CHF-, -CF<sub>2</sub>-, -CCl<sub>2</sub>-, -S-CH<sub>2</sub>-, and -N(CH<sub>3</sub>)CH<sub>2</sub>-.

12. (Canceled)

13. A method as in claim 1 wherein disease mediated by the VEGF-induced signal transduction pathway that is treated is characterized by abnormal angiogenesis or hyperpermeability processes.

14. A method as in claim 13 wherein a compound of Formula I, a salt form of a compound of Formula I, an isolated stereo-isomer of a compound of Formula I or a prodrug of a compound of Formula I is administered simultaneously with another angiogenesis inhibiting agent to a patient with such a disorder in the same formulation or in separate formulations.

15. A method as in claim 1 wherein the disease that is treated is one or more of the following conditions in humans and/or other mammals: retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; a bolos disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.

16. A method as in claim 1 wherein the disease that is treated is one or more of the following conditions in humans and/or other mammals: retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis in combination with another condition selected from the group consisting of:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) and complications due to total hip replacement.

17. A method as in claim 1 wherein the disease that is treated is one or more of the following conditions in humans and/or other mammals:

retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of:

tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*,



cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

18. A method for treating or preventing a disease in a human or other mammal mediated by a VEGF-induced signal transduction pathway, comprising administering to a human or other mammal in need thereof a compound of Formula I, a salt form of a compound of Formula I, an isomer of a compound of Formula I or a prodrug of a compound of Formula I to regulate a VEGF-mediated signal transduction cascade,



wherein A is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl groups in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring using 3 to 4 carbon atoms, the bicyclic heteroaryl group is optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro,

B is selected from the group consisting of

(i) phenyl, substituted with 1-3 substituents independently selected from the group consisting of -L-M,  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_5$  linear or branched haloalkyl,  $C_1$ - $C_3$  alkoxy, hydroxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

(ii) naphthyl, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro.

L is selected from the group consisting of:

- (a)  $-(\text{CH}_2)_m\text{-O}-(\text{CH}_2)_l-$ ,
- (b)  $-(\text{CH}_2)_m-(\text{CH}_2)_l-$ ,
- (c)  $-(\text{CH}_2)_m\text{-C(O)}-(\text{CH}_2)_l-$ ,
- (d)  $-(\text{CH}_2)_m\text{-NR}^3-(\text{CH}_2)_l-$ ,
- (e)  $-(\text{CH}_2)_m\text{-NR}^3\text{C(O)}-(\text{CH}_2)_l-$ ,
- (f)  $-(\text{CH}_2)_m\text{-S}-(\text{CH}_2)_l-$ ,
- (g)  $-(\text{CH}_2)_m\text{-C(O)NR}^3-(\text{CH}_2)_l-$ ,
- (h)  $-(\text{CH}_2)_m\text{-CF}_2-(\text{CH}_2)_l-$ ,
- (i)  $-(\text{CH}_2)_m\text{-CCl}_2-(\text{CH}_2)_l-$ ,
- (j)  $-(\text{CH}_2)_m\text{-CHF}-(\text{CH}_2)_l-$ ,
- (k)  $-(\text{CH}_2)_m\text{-CH(OH)}-(\text{CH}_2)_l-$ ;
- (l)  $-(\text{CH}_2)_m\text{-C}\equiv\text{C}-(\text{CH}_2)_l-$ ;
- (m)  $-(\text{CH}_2)_m\text{-C}=\text{C}-(\text{CH}_2)_l-$ ; and
- (n) a single bond, where m and l are 0.;
- (o)  $-(\text{CH}_2)_m\text{-CR}^4\text{R}^5-(\text{CH}_2)_l-$ ;

wherein the variables m and l are integers independently selected from 0-4,

M is selected from the group consisting of :

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro and also oxides (e.g. =O,  $-O^-$  or  $-OH$ ); and

(iv) 8 to 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro and also oxides (e.g. =O,  $-O^-$  or  $-OH$ ).

(v) saturated and partially saturated  $C_3$ - $C_6$  monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(vi) saturated and partially saturated  $C_8$ - $C_{10}$  bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro, and also oxides (e.g. =O,  $-O^-$  or  $-OH$ ); and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,

$C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano and nitro, and also oxides (e.g. =O,  $-O^-$  or  $-OH$ );

wherein each  $R^1 - R^5$  is independently selected from the group consisting of:

- (a) hydrogen,
- (b)  $C_1-C_6$  alkyl, preferably,  $C_1-C_5$  linear, branched, or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo;
- (c) phenyl;
- (d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;
- (e)  $C_1-C_3$  alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and
- (f)  $C_1-C_3$  alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo,

wherein each  $R^1 - R^5$ , when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1-C_5$  linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo,  $C_1-C_3$  alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino,  $C_1-C_3$  alkylamino,  $C_2-C_6$  dialkylamino, halogen, cyano, and nitro;

each variable  $q$  is independently selected from 0, 1, or 2;

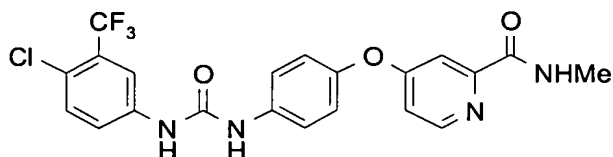
wherein B is substituted by  $-L-M$  and

M is substituted by at least one substituent selected from the group consisting of  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$  and  $C(O)NR^1R^2$ .

19. A method as in claim 18, wherein M is substituted by at least one substituent selected from the group consisting of  $-C(O)R^1$ ,  $C(O)OR^1$ , and  $C(O)NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently as defined in claim 18.

20. A method of claim 18 wherein M is substituted by  $-C(O)NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently as defined in claim 18.

21. A method of treating diseases in a human or other mammal mediated by a VEGF-induced signal transduction pathway comprising administering to a human or other mammal in need thereof the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea of the formula below or a pharmaceutically acceptable salt thereof to regulate a VEGF-mediated signal transduction cascade,



22. A method of treating diseases in a human or other mammal mediated by a VEGF-induced signal transduction pathway comprising administering to a human or other mammal in need thereof the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate to regulate a VEGF-mediated signal transduction cascade.

23. A method of claim [[1]] 18 wherein the structures of A, B and M are each, independently selected from the group consisting of phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, naphthyl, substituted naphthyl, isoquinolinyl, substituted isoquinolinyl, quinolinyl and substituted quinolinyl.

24. A method as in claim 1, wherein M is substituted by at least one substituent selected from the group consisting of  $S(O)_qR^1$ ,  $SO_2NR^1R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$  wherein q,  $R^1$  and  $R^2$  are independently as defined in claim 1.

25. A method of claim 20 wherein M is additionally substituted by one or more substituents selected from the group consisting of  $C_1$ - $C_{10}$  alkyl, up to per halo substituted  $C_1$ - $C_{10}$  alkyl, -CN, -OH, halogen,  $C_1$ - $C_{10}$  alkoxy and up to per halo substituted  $C_1$ - $C_{10}$  alkoxy.

26. A method as in claim 20 wherein L of formula I is -O-, a single bond, -S-, -NH-, -N(CH<sub>3</sub>)-, -NHCH<sub>2</sub>-, -NC<sub>2</sub>H<sub>4</sub>-, -CH<sub>2</sub>-, -C(O)-, -CH(OH)-, -NHC(O)N(CH<sub>3</sub>)CH<sub>2</sub>-, -NCH<sub>3</sub>C(O)N(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)-, C(O)N(CH<sub>3</sub>)CH<sub>2</sub>-, -NHC(O)-, -N(CH<sub>3</sub>)C(O)-,

-C(O)N(CH<sub>3</sub>)-, -C(O)NH-, -CH<sub>2</sub>O-, -CH<sub>2</sub>S-, -CH<sub>2</sub>N(CH<sub>3</sub>)-, -OCH<sub>2</sub>-, -CHF-, -CF<sub>2</sub>-, -CCl<sub>2</sub>-, -S-CH<sub>2</sub>- or -N(CH<sub>3</sub>)CH<sub>2</sub>-.

27. A method of claim 1 wherein L of formula I is selected from the group consisting of -O-, -S-, -N(R<sup>35</sup>)-, -(CH<sub>2</sub>)<sub>m</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>m</sub>O, where m= 1-3 and R<sup>35</sup> is hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, up to per halo substituted C<sub>1</sub>-C<sub>10</sub> alkyl, -CN, -OH, halogen, C<sub>1</sub>-C<sub>10</sub> alkoxy or up to per halo substituted C<sub>1</sub>-C<sub>10</sub> alkoxy.

28. A method of claim 1 wherein M is substituted by -C(O)NR<sup>1</sup>R<sup>2</sup> and R<sup>1</sup> and R<sup>2</sup> are as defined in claim 1.

29. A method of claim 18 wherein M is

- a saturated C<sub>3</sub>-C<sub>6</sub> monocyclic carbocyclic moiety selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, and cyclohexanyl;
- a saturated C<sub>8</sub>-C<sub>10</sub> bicyclic carbocyclic moiety selected from the group consisting of bicyclopentanyl and bicyclohexanyl;
- a partially saturated C<sub>3</sub>-C<sub>6</sub> monocyclic carbocyclic moiety selected from the group consisting of cyclopentenyl, cyclohexenyl and cyclohexadienyl;
- the partially saturated C<sub>8</sub>-C<sub>10</sub> bicyclic carbocyclic moiety bicyclohexenyl;
- a substituted naphthyl group selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl and tetrahydronaphthyl; or
- an 8 to 10 membered bicyclic heteroaryl group selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridiazine, cyclohexanopyridiazine, cyclopentanthiophene and cyclohexanthiophene.

30. A method as in claim 1 wherein the disease that is treated or prevented is a VEGFR-2 mediated disorder.

31. A method as in claim 1 wherein the disease that is treated or prevented is a VEGFR-1 mediated disorder.

32. (Canceled)

33. A method as in claim 1 wherein the disease that is treated or prevented is a VEGFR-3 mediated disorder.